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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,970	08/10/2001	Ashok Amin	AMIN4A	4363

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EXAMINER	
WORTMAN, DONNA C	

ART UNIT	PAPER NUMBER
1648	15

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,970	AMIN ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 1-18 were canceled and new claims 19-33 were added in Paper No. 14. Claims 19-33 are under examination.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, essentially for reasons of record in rejecting claims 1-6 previously. The claims are drawn to a method for treating any type of hepatitis (claims 19, 21, 22, 23) or a method for treating various types of viral hepatitis (claims 20, 24-27, 28-33) by administering a compound that reduces viral levels (claim 28, 30) and/or neutralizes the effect of secreted TNF alpha (claims 19-27, 29, 31) which may be either etanercept (claims 21, 25, 31) or a humanized monoclonal antibody (claims 22, 23, 26, 27, 32, 33). The specification teaches the administration of etanercept to a single patient with rheumatoid arthritis and hepatitis C, after which the patient showed an improvement in arthritis symptoms, transaminase levels and viral RNA levels. It is apparent that one of skill in the art would not be able to extrapolate from the results from administering a single compound, etanercept, to a single patient with rheumatoid arthritis and hepatitis C, to obtain a method of treating any type of hepatitis, viral or nonviral, by administering any compound that can be interpreted as neutralizing the effect of secreted TNF alpha as is claimed. Even if the claims were to be limited to

treating hepatitis C by administration of etanercept, the specification would not teach one of skill in the art how to practice the invention as claimed, since a result observed in a single patient is not seen to enable a treatment method. The state of the art at or near the time the invention was made is properly considered in evaluating enablement. Campbell et al. (European Journal of Gastroenterology and Hepatology 13(2):191-192, 2001), of record (not prior art), disclose treatment of a patient with Crohn's disease, who also had chronic hepatitis C, with infliximab. Campbell et al. report no change in the raised level of the liver enzyme alanine aminotransferase and, despite the fact that the PCR for HCV was reported to be negative at 16 weeks follow-up, Campbell et al. do not suggest that infliximab is a treatment for hepatitis C, but rather interpret this result observed in a single patient differently: "... it would appear that in this particular case infliximab therapy was not detrimental to ongoing HCV infection" (page 192). Campbell provides evidence that a single case report does not provide those of skill in the art with sufficient teaching to practice a method of treatment, since the lack of a bad result in a single case cannot be extrapolated to a reasonable expectation for success in obtaining a generally beneficial result as is required in order to enable a treatment method.

Applicant has argued that paragraph 0019 of the specification states that TNF neutralizing compounds were found to reverse the clinical symptoms associated with hepatitis, including normalization of liver enzymes and decrease in serum viral levels, and refers to a Declaration of Dr. Ashok Amin and Dr. Steven Abramson describing in more detail the treatment of patients described in paragraph 0019 in the specification, pointing to the results shown in Table 1 of the Declaration as supporting the conclusion

that patients treated with a compound that neutralizes the effect of secreted TNF alpha showed improvement resulting from the treatment.

Applicant's arguments and the Declaration of the inventors have both been considered but not found persuasive for the following reasons. The Declaration under 37 CFR 1.132 filed 18 July 2003 is insufficient to overcome the rejection of claims 19-33, which is essentially the same rejection as that applied to claims 1-17 based upon 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, as set forth in the last Office action. The Declaration does not set forth sufficient facts to allow one to evaluate what subject matter is enabled by the specification at paragraphs [0016]-[0018] and [0019], as the relationship between "Patient 1" described in the Declaration at page 5, second full paragraph, through the end of the paragraph bridging pages 5 and 6, and in Table 1 at page 7, and what is disclosed in the specification at [0016]-[0018] is not stated. There is no stated relationship between the results given in Tables 1 and 2 and the specification at paragraph [0019]. While Applicant may provide evidence, e.g., by submitting a Declaration, to demonstrate that the disclosure enables the claimed invention, Applicant may not rely on a Declaration to provide what the specification lacks. The Declaration is rather confusing since it refers to "seven patients" described in Table 1 as patients 2-8; to patients 2 and 3 as having decrease in HCV RNA following Etanercept therapy; and to the "remaining six" patients as showing no response or having inadequate data. It would appear that results for the remaining

five, not six, patients 4-8 are actually presented in Table 2. Further, the showing of the Declaration is not commensurate in scope with what is claimed, since the Declaration presents data only for patients having HCV who have been treated with etanercept. No pending claims are limited to treatment of patients having HCV who have been treated with etanercept. In addition, Declarants' statements at the paragraph bridging pages 4 and 5 through the second full paragraph of page 5 of the Declaration would seem to provide support for a finding of unpredictability in the art of treating hepatitis C with etanercept, indicating that there is a question as to the reasonable expectation for success in doing so.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 28 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,939,423 to Karlin et al., cited on PTO 892, attached. Karlin discloses a method for treating hepatitis B by administering an antiviral amount of thymosin alpha 1 and an antiviral amount of famciclovir, anticipating the subject matter of claims 28 and 30.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 20, 24, 28, 29, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by The Merck Manual of Diagnosis and Therapy (Beers et al., Eds., Seventeenth Edition, published by Merck Research Laboratories, 1999) pages 384-386, of record, essentially for reasons of record. The Merck Manual discloses treatment of autoimmune hepatitis with corticosteroids, anticipating the subject matter of claim 19, and treatment of hepatitis B and hepatitis C with interferon alpha, and discloses that both treatments result in reduction of inflammation, anticipating the subject matter of claims 19, 20, 24, 28, 29, and 30. Since the cited claims do not require direct interaction with TNF or TNF receptor, the hepatitis treatments disclosed by the Merck Manual are deemed to anticipate the claims.

Applicant has argued that the present claims recite neutralizing the effect of secreted TNF alpha or reducing the viral load in a patient, which is not taught nor suggested by The Merck Manual which states that using interferon to treat hepatitis has been relatively disappointing. Applicant has argued that treating patients with viral hepatitis with a compound that neutralizes the effect of secreted TNF alpha has met with unexpected success and has submitted copies of various articles and abstracts in support, pointing out that the consensus among physicians as late as 2002 was that TNF alpha blocking agents should not be used to treat patients with serious infections like hepatitis.

These arguments have been considered but not found persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that features upon which applicant relies (i.e., treating patients with viral hepatitis) are not recited in rejected claim 19. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, Applicant's comments in Paper No. 6 indicate that a compound that reduces inflammation is included within the scope of a compound that neutralizes the effect of secreted TNF alpha, and includes corticosteroids and interferon alpha. Applicant's argument that interferon treatment has been relatively disappointing is not found persuasive, since, despite the fact that interferon treatment of viral hepatitis is not uniformly successful, it remains a conventional treatment for both hepatitis B and C.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw